GENETECH Oncology and IDEC Pharmaceuticals
INVESTIGATOR INITIATED PROTOCOL CONCEPT WORKSHEET

DATE	January 18, 1998
STUDY TITLE	Phase I Study of Thrice Weekly Administration of IDEC-C2B8 in Patients with Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)
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Sub-Investigators	Yes (see page 2)
Scientific Rationale	To date, low responses (CR + PR 12%) have been observed with IDEC-C2B8 in previously treated patients with CLL/SLL. These patients have high tumor bulk, lower surface CD20 expression, and lower serum antibody plasma $t_{1/2}$. Before phase II studies are initiated with IDEC-C2B8 as a single agent in CLL, an adequate dose and schedule of administration must be determined. Frequent (thrice weekly) administration of IDEC-C2B8 should ensure continuous high serum concentrations of antibody in CLL/SLL patients with large tumor loads. Additionally, this schedule might facilitate rapid tumor reduction which is a known favorable therapeutic prognostic factor in other types of leukemia and non-Hodgkin's lymphoma. It is hoped that this schedule could be utilized in subsequent phase II studies of untreated and previously treated patients with CLL that are currently being planned by CALGB (chaired by investigator) and others.
Study Objective	To examine the feasibility and safety of administering IDEC-C2B8 thrice weekly in patients with B-cell chronic lymphocytic leukemia or small lymphocytic lymphoma
Study Endpoint	(1) Irreversible grade 3-5 non-hematologic toxicity (CALGB) (2) Attainment of > than the mean IDEC-C2B8 serum peak/trough concentration during weeks 2-4 that was observed in responding patients on the Pivotal IDEC-C2B8 phase III study.
Treatment Design	Dose Level 1 250 mg/m2 IV on Monday/Wednesday/Friday x 4 wks Dose Level 2 375 mg/m2 IV on Monday/Wednesday/Friday x 4 wks Infusion prophylaxis will include benadryl 50 mg iv; tylenol 650mg po demerol 25 mg iv; and pherergan 25 mg iv Standard Phase I study design will be utilized. Three patients will be enrolled at 250 mg/m2 dose. If DLT does not occur, 3 additional patients will be enrolled to cohort 2. If DLT toxicity is not observed, 3 additional patients will be enrolled to cohort 2. If < 2 DLT occur in these patients, this will be the recommended phase II dose for CLL provided study endpoint (2) is met. Pre-treatment and Post-treatment pharmacokinetics and molecular pharmacodynamic studies would be performed.
Number of Patients	9-12
TimeLine	IRB Approval 4/1/98 First Patient Enrolled 4/15/98 Last Patient Enrolled 8/1/98
Support Requested	Drug Yes approximately 60 g Pharmacokinetics analysis Yes Grant* Yes

*Negotiable

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Dose-Escalation Feasibility Study of Rituximab Administered Thrice Weekly to Patients with Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

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0.0 STUDY RATIONALE:

This is a dose-escalation, feasibility trial of rituximab in a thrice weekly schedule for patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). This study is proposed based upon the unique pharmacokinetics previously observed with rituximab administration in SLL and the absence of pharmacokinetic data in CLL.

1.0 OBJECTIVES

(i) To determine the feasibility and toxicity of Rituximab administration in a thrice weekly schedule for a total of 4 weeks in patients with CLL and SLL.

(ii) To investigate the pharmacokinetics and cellular pharmacodynamics of Rituximab administered on this schedule.

(iii) To preliminarily assess if rituximab has anti-tumor activity with this novel schedule of administration.

Schema

Patient with CLL or SLL

Rituximab Therapy: Cohort 1 (250 mg/m^2) Thrice Weekly x 4 weeks*[1,2]
Cohort 2 (375 mg/m^2) Thrice Weekly x 4 weeks*[1,2]

***First Day of Therapy dose will be 100 mg total dose**
[1]All patients will receive allopurinol 300 mg po day 1-14 of therapy
[2]Cytokine, pharmacokinetic and pharmacodynamic studies will be done on all patients

Primary Endpoint :	**Feasibility of Administration**
Secondary Endpoints :	**Pharmacokinetics** **Cellular and Cytokine Pharmacodynamics** **Anti-tumor activity**

2.0 BACKGROUND

2.1 Chronic Lymphocytic Leukemia: Current Status

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia occurring in the western hemisphere and accounts for 25% of all leukemias. Approximately 95% of CLL is of B-cell lineage and occurs most commonly in the elderly. Despite the greater than 10-year life expectancy in early stage patients, CLL remains an incurable illness (1,2). Patients progressing onto or diagnosed with more advanced stage CLL have a median survival between 18 months to 3 years. Regardless of the stage, patients with CLL also have an impaired immune system as demonstrated by defects in complement, antibody-dependent cellular cytotoxicity (ADCC), cellular immunity, and most important, hypogammaglobulinia that becomes more pronounced with disease progression (3-9). Such impaired immune function leads to the well-characterized natural history of CLL with frequent infections, an increased risk of secondary malignancies, and autoimmune complications (10-12).

Patients with low-risk, early stage CLL can be followed closely, as there is no survival benefit associated with early intervention. With disease symptoms or progressive cytopenias, patients previously were treated with oral alkylating agents with or without prednisone. Responses to alkylating agents are not durable, and only rarely are associated with morphologic complete remission. With the advent of fludarabine, treatment of CLL has undergone a metamorphosis. Fludarabine is a nucleoside analog that inhibits DNA polymerase, ribonucleotide reductase, and promotes apoptosis (programmed cell death) in malignant CLL cells and in normal T-cells (CD4+ > CD8+). Treatment with fludarabine yields a 31%-57% response rate in alkylator-resistant CLL patients (13-14) and a 79% response rate in untreated patients (15). These responses include a high number of complete remissions in both untreated (33%) and previously treated patients (13%) which were rare with previously used alkylator-based regimens. However, opportunistic infections not previously observed in CLL were reported, and are likely reflective of concurrently applied therapies and heavy pre-treatment with other chemotherapeutic agents (16). Given the promising response data and manageable toxicity with fludarabine, CALGB and other cooperative groups undertook phase III studies to evaluate fludarabine's efficacy and toxicity as compared with either alkylator or combination-alkylator based regimens. Results from several of these phase III studies of untreated CLL patients have recently been published. Hiddemann et al. noted similar response rates between fludarabine and CAP (cyclophosphamide, adriamycin, and prednisone), but observed a significantly prolonged disease-free survival in the former group of patients (17). Results from CALGB 9011 demonstrated a significantly higher CR rate (27% vs. 3%), CR + PR (70% vs. 40%), and disease-free survival (33 months vs. 17 months) in patients receiving fludarabine as compared with chlorambucil (18). These data have elevated fludarabine to an acceptable first-line therapeutic option in the treatment of symptomatic CLL.

2.2 Chronic Lymphocytic Leukemia: Future Directions

Attempts to improve on the treatment results of single agent fludarabine are currently ongoing. Despite the encouraging high complete response rates with combination regimens such as cyclophosphamide and fludarabine (19), a uniformly higher toxicity in terms of either myelosuppression, cellular immune dysfunction, or pulmonary toxicity has been observed when other agents such as prednisone, chlorambucil, or deoxycoformycin have been combined with fludarabine (20-23). Other agents such as 9-aminocamptothecin, bryostatin, and gemcitabine are currently under investigation in previously-treated CLL. Maintenance therapy with alfa interferon following fludarabine has been investigated, and has been found to be ineffective in either improving maximal response or immune dysfunction post-treatment (24). Allogeneic and autologous bone marrow and stem cell transplant have generated exciting results, but are not therapeutic options for the majority of elderly patients with CLL. Several attempts at immunotherapy with monoclonal antibodies have been attempted in CLL patients (25-27). The outcome of these studies has been impaired by the lack of ADCC with murine antibodies, the development of human antibody to murine antibody reactions, large serum load of free antigen, anaphylactic reactions, and the inability to obtain sufficient antibody for large clinical trials. Due to the biologic limitations of murine derived-antibodies, attempts to combine human constant regions and murine binding sites (i.e., chimeric antibodies) have been pursued. These chimeric antibodies have a prolonged half life, along with the ability to induce both complement and effector cell tumor lysis. One such antibody is Rituximab, a chimeric antibody directed against CD20. CD20 is a B-lymphocyte derived antigen that is expressed on pre-B-cells to lymphoplasmacytic lymphocytes but is not present on stem cells or other non-hematopoetic cells. CD20 is neither detectable in the serum nor internalized after binding to idiospecific antibody. CD20 is expressed on the majority of B-cell NHL and virtually 100% of CLL patients (although dim). Pre-clinical studies utilizing Rituximab demonstrated that this chimeric antibody is effective in lysing cells via both human complement-mediated cytotoxicity and ADCC (28). Cynomolgus monkeys have been treated with escalating doses of Rituximab. Pathologic staging of bone marrow and lymph nodes post-therapy revealed marked depletion of CD20+ lymphocytes in the absence of demonstrable toxicity.

The high expression of CD20 in B-cell NHL and promising pre-clinical results have led to phase I and II studies with Rituximab. Maloney et al. performed a phase I study of Rituximab in fifteen patients with relapsed NHL (29). Two partial and four minimal responses were observed with Rituximab. Immunologic monitoring during and after CD20 antibody infusion revealed no change in serum immunoglobulin levels and no excessive infections. A phase II study of Rituximab (375 $mg/m^2/wk$ x 4) followed in 34 patients with heavily pre-treated low-grade NHL demonstrating a 50% response rate (three CR and eleven PR) with a median response duration of 10.3 months (30). Adverse events included rigors, bronchospasm, fatigue, pain, and cytopenias (the later of which were grade three or greater in only 7% of patients). Importantly, immunoglobulin levels remained stable and there were only eleven infections (ten of

which were mild). This study was verified by a larger phase II/III study of 166 patients with previously treated low-grade NHL (31). Overall response rate in this study was 48% (6% CR and 42% PR) with the majority of responding patients converting to a bone marrow negative BCL-2 status by 3 months post completion of therapy. Due to *in vitro* data (32) suggesting that Rituximab can chemosensitize chemotherapy-resistant NHL cell lines and the absence of competing toxicities, Czuczman et al. initiated a study of interdigitated Rituximab with CHOP chemotherapy in low-grade NHL (33). The overall response rate for patients completing therapy was 100% (60% CR and 40% PR). Notably, seven out of eight patients with a positive pre-treatment BCL-2 who completed therapy with Rituximab /CHOP became BCL-2 negative. BCL-2 conversion is generally not observed with CHOP therapy alone. Preliminary data from an ongoing phase III study of single agent Rituximab in relapsed NHL demonstrated six of twelve patients completing therapy have converted from BCL-2 positive to BCL-2 negative using nested PCR techniques (34). Based on these data, additional large phase III studies of Rituximab in NHL are being planned by CALGB and other cooperative groups.

2.3 Data on Rituximab Administration in CLL, SLL, and PLL

In contrast to that with follicular lymphoma, there is little published experience about the therapeutic efficacy of rituximab in the treatment of CLL, SLL, and PLL. Available published data is mainly derived from the phase II NHL studies that included patients with SLL without peripheral blood lymphocytosis. The later point can not be underestimated, as toxicity and pharmacokinetics might be quite different in CLL, SLL, and PLL where a large proportion of tumor cells are circulating in the peripheral blood and bone marrow, thus increasing the potential for rapid tumor-antibody binding and clearance from the plasma. If response to an agent (i.e. rituximab) were dependent upon plasma concentration, this might alter the efficacy of the agent. A discussion follows outlining the current experience with rituximab in CLL/SLL with subsequent study justification of a thrice weekly schedule of administration in these diseases.

In the pivotal multiple-dose study, rituximab was administered once weekly for 4 treatments. Only patients with low-grade lymphoma who did not have a circulating lymphocytosis were allowed to enroll on this study. The overall response rate for the 166 patients enrolled on this study was 48%. When response was broken down by the International Working Formulation (IWF) classification, response was significantly lower in the 33 patients with SLL (12% versus 58%; $p<0.001$) as compared to those with patients with IWF B, C, or D histology. (35) However, it is notable that 76% of these patients did gain some benefit (i.e. regression in tumor size or relief of B-symptoms that did fulfill criteria for PR). (36) Other factors predicting for an inferior response in this study included bone marrow involvement ($p=0.01$) and absence of bcl-2 lymphocyte expression (i.e. non-follicular morphology). (35) Pharmacokinetic studies were performed on a limited number of patients enrolled on this pivotal study and demonstrated a strong correlation of mean plasma antibody concentration with response. This is not surprising, as in the pre-clinical animal studies, clearance of

lymphocytes occurred in dose-responsive fashion, with blood, bone marrow, lymph nodes/spleen requiring progressively higher rituximab antibody plasma concentrations.(35) Pharmacokinetic studies of patients with SLL demonstrated a significantly lower pre-treatment plasma trough concentration of rituximab before the second and forth infusion, and at the one-week, one-month, and three-month post-treatment as compared to other low-grade histologies. (35) The reason for these altered pharmacokinetics is uncertain, with some hypothesizing that a larger pool of peripheral blood and bone marrow tumor cell involvement exists in patients with SLL that serves as a sink for antibody. Other possibilities include increased clearance in the absence of tumor binding given the often dim expression of this surface antigen on SLL tumor cells or accelerated antibody clearance even in the presence of effective tumor binding. Nonetheless, these data suggest that a once weekly schedule of rituximab in SLL (and related CLL) is not optimal.

A second study administering rituximab once weekly for 8 weeks in NHL has been preliminarily reported (36). In this study seven patients with small lymphocytic lymphoma were examined in a subset analysis with three (43%) attaining a partial or complete response. Although the patient number in this study is quite small, this suggests that additional dosing of rituximab might improve response rate as observed in the pivotal study. Pharmacokinetic and pharmacodynamic data are currently unavailable from this study. To date, no pharmacokinetic data exists from rituximab administration in patients with CLL. As there is little suggestion of prolongation of rituximab half life in SLL, (35) this suggests that antibody accumulation does not occur in this histologic subtype. Weekly administration of rituximab for longer periods of time (i.e. 8 versus 4 weeks) therefore might not lead to pre-treament plasma concentrations that are lympholytic. An alternative approach, that being shortening the interval of rituximab administration might prove to be more effective.

As patients with CLL and SLL often have high circulating peripheral blood tumor cells, a propensity for increased early adverse events (i.e. infusion reactions) and rapid tumor lysis might exist with rituximab administration. We have indeed documented this in two index cases treated at Walter Reed Army Medical Center and 3 additional patients reported to IDEC Pharmaceuticals. (37) The clinical features of these patients included evidence of rapid decrease in blood tumor cells, mild laboratory evidence of tumor lysis, infusion-related toxicity (bronchospasm, rigors, chills, and fever), and thrombocytopenia. As a consequence of this observation, we have recently initiated a standard SOP at Walter Reed for patients with elevated blood tumor cells receiving rituximab based upon the above experience. Patients receive 100 mg of their scheduled dose on the first day and complete the remaining dose of rituximab on day 2 or 3 of treatment. This has been applied to 2 patients with CLL without significant morbidity (but ongoing documentation of efficacy). Similarly, rituximab (375 mg/m^2) has been administered concurrently with fludarabine (days 1 and 4) of therapy to five patients on the ongoing CALGB 9712, a phase II study of untreated, symptomatic CLL. All patients have experienced non-dose limiting infusion-related toxicity and one patient has had transient (2 days) grade 4 thrombocytopenia with the first infusion. (Personnel

communication, John C. Byrd M.D.) To allow recovery from possible transient thrombocytopenia, we will allow a one day interval between the first and second dose of treatment in this study.

2.4 Justification of Thrice Weekly Schedule of Rituximab in CLL, SLL, and PLL

From the data outlined above, one can conclude that the once weekly schedule of rituximab adminstration in CLL/SLL is not optimal and might explain the lower responses that have been observed in this subset of patients. Optimizing the trough concentration of rituximab in CLL/SLL will require both pharmacokinetic studies and examination of alternative schedule of administration. We have chosen the thrice weekly schedule based upon: (1) shorter half-life of rituximab in SLL (2) pre-clinical *in vivo* studies demonstrating the importance of higher plasma rituximab concentration for response in bone marrow and lymph nodes/spleen (3) this being "the most ideal" schedule of antibody administration of campath-1H (another chimeric monoclonal antibody with a similar $_{t1/2}$ as compared to rituximab) in CLL. Based on our experience in patients with high circulating peripheral blood tumor counts, we would expect infusion reactions to be more frequent, and for mild, non-dose limiting cytopenias (particularly thrombocytopenia) to occur in patients experiencing this. (35) We will therefore utilize a small dose (100 mg) on the first day of treatment and subsequently escalate to the intended dose on the next subsequent treatment. If the thrice weekly schedule of administration proves to be feasible in CLL and SLL patients, a subsequent phase II study may be considered at our institution or as third added arm to the ongoing CALGB study (chaired by the PI of this study)

2.5 Preliminary Justification for Pharmacodynamic Studies Proposed

To date, minimal data exists regarding predictive factors for response to rituximab in patients with SLL and CLL. Laboratory studies have demonstrated that rituximab is a specific immunotherapy requiring tumor CD20 expression for activity.(32) Similar in vivo observations have been made with another humanized chimeric monoclonal antibody (campath-1H) in CLL and PLL (38). Our working hypothesis is that patients whose CLL/SLL cells express CD20 brightly will have rapid peripheral tumor lysis, a shorter plasma half-life, significant infusion-related toxicity, and ultimately a better response to rituximab. Although the sample size in this study is small, we propose to preliminarily examine quantitative CD20 expression in the tumor lymphocytes and correlate this with the above mentioned pharmacodynamic variables. Additionally, we will assess the relative percentage of CLL/SLL tumor cells expressing CD20 prior to and at completion of rituximab therapy. These flow cytometric studies will be performed by a central laboratory (to be identified) utilizing standard flow cytometric techniques.

In patients with low-grade lymphoma, rituximab produces infusion related toxicity including fever, rigors and chills in greater than 50% of patients treated. These infusion-related symptoms generally are less significant with subsequent treatments. As outlined above, these symptoms might be more frequent and severe in patients who

have high circulating blood tumor cell counts. There has been no investigations published to date that explain why this toxicity develops after rituximab therapy. Studies with another humanized chimeric monoclonal antibody campath-1H, have been associated with similar infusion-related toxicities in several diseases. Studies by Wing and colleagues (39,40) have demonstrated that incubation of whole blood *ex vivo* with campath-1H results in predictable rise in plasma concentrations of tumor necrosis factor alpha (TNF-alpha), interferon-gamma (IFN-gamma), and interleukin-6 (IL-6) at 2, 4, and 6 hours post-treatment. Similar findings have been observed *in vivo* in patients with multiple sclerosis and have correlated with both infusion-related toxicities and reversible exacerbations of existing neurologic symptoms. Others have reported similar cytokine release with campath-1H administration in other disorders (i.e. rheumatoid arthritis and leukemia/lymphoma patients) without neurologic symptoms suggesting that a pre-existing neurologic findings may predispose to this toxicity. Further studies by this group demonstrated that CD16 ligation on NK cells in part explained this cytokine release *in vivo*. Given the similar rapid onset of symptoms *in vivo* with rituximab administration which is clinically identical to that observed with campath-1H, we hypothesize that a similar NK cell dependent cytokine release is occurring. This might also be the explanation of the transient thrombocytopenia observed with initial rituximab administration. We propose to do a pilot study examining concurrent in vivo and ex vivo cytokine release following treatment with rituximab. Whole blood will be incubated with media or rituximab at 100 μg/ml, 500 μg/ml and 1000 μg/ml. Plasma will be isolated at 2, 4, and 6 hours and frozen at -70°C. These samples will be analyzed for IL-1, IL-2, IL-6, IL-8, TNF-alpha, and IFN-gamma at each of these time points. Similarly, blood samples will be drawn pre-treatment, 2 hours, 4 hours, 6 hours post-treatment and at the time of infusion-related toxicity during the first two treatments with rituximab. A similar panel of cytokines (IL-1, IL-2, IL-6, IL-8, TNF-alpha, and IFN-gamma) will be obtained at each of these time points. Cytokine expression both *in vivo* and *ex vivo* will be correlated with pharmcodynamic and pharmacokinetic variables. If cytokine release is noted with ex vivo administration, additional studies as performed by Wing and colleagues might be performed (39,40) It is hoped that this investigation will identify both the source of rituximab induced infusion-related toxicity and an accurate way to predict for this clinically significant event. Additionally, if the etiology is mediated predominantly by one cytokine such as TNF-alpha, subsequent targeted abrogation of this effect might be clinically possible with concurrent treatment with the TNF-alpha ligand that will soon be commercially available for clinical use.

2.6 Inclusion of Women and Minorities

Chronic lymphocytic leukemia has a 2:1 male-to-female frequency and is more frequently observed in caucasians compared to minorities. A recently completed phase III study in untreated CLL patients performed by CALGB accrued a total of 539 patients of which 32% were female. Race composition of this study was 88% Caucasian, 10% African-American, 1% Hispanic, and 1% other. A similar

composition is expected on the present study. Patients who meet the eligibility criteria will be included on this study without regard to gender, race, or ethnicity

3.0 ON-STUDY GUIDELINES

This clinical trial can fulfill its objectives only if patients appropriate for the trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy and, therefore, only enroll patients for which the agents administered are appropriate. Although they will not be considered as formal eligibility criteria, as part of this decision-making process physicians should recognize that the following may increase the risk to the patient entering this protocol:

- Other serious illnesses which would limit survival to <3 months, or psychiatric condition which would prevent compliance with treatment or informed consent.
- Uncontrolled or severe cardiovascular disease, pulmonary disease, or infection, which in the opinion of the treating physician, would make this protocol treatment unreasonably hazardous for the patient.

3.1 Inclusion criteria

3.1.1 Patients must have histologically documented CLL or SLL.

3.1.2 Patient's tumor lymphocyte cells must express CD20

3.1.3 Patients must have ECOG performance status ≤ 3.

3.1.4 Patients must have a life expectancy of at least 12 weeks.

3.1.5 Patients must have a serum creatinine of $\leq$ 3.0 mg/dl.

3.1.6 Patients must be 18 years of age or older.

3.1.7 Patients must provide written informed consent.

3.1.8 Patients must have recovered from toxicity of previously administered radiotherapy or chemotherapy.

3.2 Exclusion criteria

3.2.1 As rituximab may be harmful to the developing fetus or nursing infant women must not be breastfeeding and must have a documented negative pregnancy test (if ovulating). An effective method of contraception should be used while on study.

3.2.2 Patients with active infections requiring oral or intravenous antibiotics are not eligible for entry onto the study until resolution of the infection.

3.2.3 Patients with a previous allergic reaction to rituximab will be excluded from this study

4.0 REGISTRATION OF PATIENTS

All patients eligible for this dose-escalation study should be discussed with the principal investigator (or local co-principal investigator) before entry onto the study. The on-study form should be completed, the on-study requirements for laboratory work and evaluation fulfilled (section 8.0), and informed consent obtained (Appendix 3).

The study will be conducted at the Walter Reed Army Medical Center and the Johns Hopkins Oncology Center. Dr. Byrd is the protocol chairman and will be liaison with IDEC Pharmaceuticals and Genentech, Incorporated. He will coordinate the protocol management at Walter Reed in concert with the effort of Dr. Ian Flinn at Johns Hopkins Oncology Center. Patients will be registered by faxing an eligibility screening sheet and a signed informed consent sheet to Kathy Park R.N. at 202-782-9243.

To ensure timely communication of treatment tolerance, the principal investigator at each institution will discuss the progress of each patient once weekly. Adverse events will be communicated to Dr Byrd directly by the treating physician or his designee to ensure safe treatment of other patients in the study and timely communication of adverse events with the IDEC Pharmaceuticals, Genentech, Incorporated, WRAMC Department of Clinical Investigation, and the Joint Committee on Clinical Investigation.

5.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

5.1 Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

5.2 Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

5.3 The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

5.4 Allopurinol (Lopurin, Zyloprim)

AVAILABILITY

Commercially available as 100 mg and 300 mg tablets.

STORAGE AND STABILITY

Store tablets in a tight container at 15-308C.

ADMINISTRATION

Administer by mouth. Fluid intake should be sufficient to yield a daily urine output of 2 liters.

TOXICITY

Dermatologic toxicity, including pruritic maculopapular rash, urticaria, exfoliative dermatitis, and hemorrhagic dermatides which may be accompanied by alopecia, fever, and malaise. Stevens-Johnson syndrome (exfoliative dermatitis with mucous membrane involvement) has been reported. Patients with compromised renal function may be at a greater risk of development of rash. Skin reactions may be delayed as long as two years after initiation of therapy. Gastrointestinal side effects, including nausea, diarrhea, and abdominal pain may occur. Drowsiness may also occur.

DRUG INTERACTIONS

Administration of allopurinol with ampicillin or amoxicillin may increase the risk of skin rash. Allopurinol and chlorpropamide may result in an increased risk of hypoglycemia, whereas allopurinol with bactrim may increase the risk of thrombocytopenia.

5.6 Rituximab Monoclonal Antibody (Rituxan, IDEC-C2B8)

AVAILABILITY

The antibody for this trial will be supplied by Genentech and IDEC Pharmaceuticals.

Rituximab is supplied in 10 ml and 50 ml single-use vials with no preservative added. The vials contain 100 or 500 mg of antibody in a sodium chloride solution (pH 6.5) containing polysorbate 80 and sodium citrate at a concentration of 10.0 mg/ml.

STORAGE AND STABILITY

Vial labels contain an expiration date. Each lot undergoes periodic shelf-life stability testing, and investigators will be notified by IDEC Pharmaceuticals when any particular lot is no longer acceptable for clinical use.

PREPARATION

Because Rituximab is a protein, it is essential to handle the product gently and to avoid foaming during product preparation and administration as this may lead to denaturing of the active antibody. Rituximab should be prepared as follows:

a. Refrigerate Rituximab (2-8°C) prior to use. All other materials need not be refrigerated;

b. Use sterile, non-pyrogenic, disposable containers, syringes, needles, stopcocks, and transfer tubing, etc.

c. Transfer of the Rituximab from the glass vial should be made by using a suitable sterile graduated syringe and large gauge needle;

d. Transfer the appropriate amount of Rituximab from the graduated syringe, into a partially filled IV pack containing sterile, pyrogen-free 0.9% sodium chloride solution, USP (saline solution). **The final concentration of Rituximab in saline solution may be between 1 and 4mg/mL.** Mix by inverting the bag gently. DO NOT USE A VACUUM APPARATUS to transfer the product from the syringe to the plastic bag.

e. Place an IV administration set into the outflow port of the bag containing the infusion solution.

ADMINISTRATION

The administration of Rituximab will be accomplished by slow IV infusion. DO NOT ADMINISTER as an intravenous push or bolus. IV pumps may be used with the IDEC-C2B8 infusion. Do not infuse Rituximab concomitantly with another IV solution (except nomal saline or D_5W) or IV medications. Prime line with the IDEC-C2B8 solution such that approximately 30 ml are delivered. This will saturate the filter and tubing. If delay in adminstration occurs after the infusion solution is prepared, the properly identified container may be refrigerated at 2-8 °C for up to six hours prior to initiating the administration of the product.

TOXICITY

Hypersensitivity reactions (including instances of throat swelling, rash, urticaria, bronchospasm, and angioedema), fever, nausea, vomiting, rigors, chills, fatigue, headache, dizziness, asthenia, rhinitis, hypotension, thrombocytopenia, leukopenia, anemia, pruritis, diarrhea, respiratory symptoms, myalgias, arthralgias, and pain during injection. Most of these toxicities have occurred during the initial infusion and have been observed in patients with bulky tumor or high blood tumor cell counts. However; toxicities have been routinely observed in all patient groups. Self-limited infections (< 10% patients treated) have been observed in patients receiving IDEC-C2B8. Opportunistic infections (papovavirus, Listeria monocyotgenes, Herpes zoster) and hepatitis-B reactivation have been rarely observed either during or after rituximab therapy.

6.0 TREATMENT PLAN

6.1 Baseline assessment: Patients will have screening assessment (history, physical examination and blood tests) within 10 days of beginning treatment. Assessment of measurable disease (CT or MRI) and bone marrow biopsy may be performed within 4 weeks of treatment. Study parameters are listed in section 8. Tumor measurement criteria are specified in section 10.

6.2 Schedule of Administration

For the first infusion:

All patients will receive diphenhydramine 50 mg IVP, and tylenol 650 mg po 30 minutes prior to initiation of rituximab

All patients will receive a 100 mg dose (regardless of weight/BSA) of rituximab. The infusion rate will be 25 mg/hr and dose escalation will NOT occur.

If rigors occur, rituximab administration should cease temporarily and meperidine 25 mg IVP and promethazine 12.5 mg IVP should be administered.

If transient bronchospasm occurs, rituximab administration should be interupted and the patient should be treated hydrocortisone 100 mg and albuterol (or other B_2 agonist) inhaler. Once this has returned to grade 1 in severity, rituximab administration can resume.

Subsequent infusions

All patients will receive diphenhydramine 50 mg IVP, and tylenol 650 mg po 30 minutes prior to initiation of rituximab

All patients will receive the dose of rituximab as appropriate to the cohort they are assigned to. This can be administered at an initial rate of 50 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr

If rigors occur, rituximab administration should cease temporarily and meperidine 25 mg IVP and promethazine 12.5 mg IVP should be administered.

If transient bronchospasm occurs, rituximab administration should be interupted and the patient should be treated hydrocortisone 100 mg and albuterol (or other B_2 agonist) inhaler. Once this has returned to grade 1 in severity, rituximab administration can resume.

6.3 Ancillary Therapy

All patients should receive allopurinol 300 mg p.o. qd for the first 14 days of treatment.

Prophylactic antibiotics are left to the treating physician. Patients should receive *full supportive care*, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. Additionally, patients should receive instruction regarding both the appearance of and clinical significance of varicella zoster lesions and should be provided with a copy of the zoster teaching sheet. All blood products should

be irradiated to prevent transfusion-associated graft versus host disease. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the flow sheets.

6.4 Dose Limiting Toxicity

For the purposes of the protocol dose limiting toxicities will be defined as non-hematologic toxicity of grade 3 or greater severity (except transient bronchospasm in the absence of urticaria that is reversible with the interventions outlined previously). In some case grade 2 toxicity (e.g. irreversible renal, chronic pulmonary, neurologic, cardiac, and local toxicities) will be considered dose limiting toxicities. Hematologic toxicity will not be considered dose-limiting. Additionally, The NCI Criteria (Appendix 4) will be used to characterize toxicity. These criteria will be supplemented by a Grading Scheme for CLL studies (Appendix 5).

6.5 Maximum Feasible Dose

The maximum feasible dose is the highest safely tolerated dose. This will be the dosage level where some dose limiting toxicity occurs that is reversible and does not subject the patients to excessive risks or discomfort. These toxicities are referred to a dose limiting toxicities. As rituximab is minimally myelosuppressive and has a favorable toxicity profile as compared to most chemotherapy agents, it is quite likely that this dose will not be achieved in this study.

6.6 Recommended Phase II Dose

This is the dose level below the maximum tolerated dose or the highest dose outlined below (i.e. 525 mg/m^2). At least 10 patients will be treated at this dose to characterize fully the pharmacokinetics of this schedule in CLL and to allow sufficient patient numbers to adequately evaluate the exploratory pharmacodynamic studies.

6.7 Dose Escalation Scheme

Three patients will be treated at the first dose level. It is anticipated that this will be well tolerated as CALGB 9712 is administering two 375 mg/m^2 doses of rituximab during the first week of therapy concurrent with fludarabine. This has been well tolerated to date in five patients with only one transient episode of grade 4 thrombocytopenia that resolved within 2 days. (personnel communication, J.C. Byrd)

Doses will be escalated as follows:

Dose Level	Dose
-1	200 mg/m^2
1	250 mg/m^2
2	375 mg/m^2

Patients will initially be treated at their assigned dose (after the first treatment) as outlined above on Wednesday, and Friday and then subsequently on Monday, Wednesday, and Friday for 3 additional weeks (i.e. 12 total treatments with rituximab). Three patients will be treated at a dose level. If none experiences a dose limiting toxicity then the next dose level will be used for subsequent cohort of 3 patients. If at any dose level one of the 3 patients experiences a dose limiting toxicity then 3 additional patients will be accrued to that dose level. If none of these 3 additional patients experience a dose limiting toxicity then the dose will be escalated. Otherwise the maximum tolerated dose has been exceeded and an additional 3-6 patients will be treated at the previous dose level (to include a minimum of 10 patients and maximum of 25 patients).

6.8 Intra-patient Dose Reduction or Escalation

A patient who experiences dose limiting toxicity in the study may remain on study provided the toxicity has reversed completely within 4 weeks. They should be treated at the next lowest dose level.

No intra-patient dose escalation will occur in this study.

6.9 Disease response

Patients will undergo a detailed clinical evaluation (physical exam with lymph node, liver, and spleen measurement; CBC with manual differential) at completion of therapy. They will be observed for an additional 2 months and will then undergo a bone marrow and CT scan. Patients responding to rituximab will have a follow-up evaluation every 3 months for 1 year (end of study). Patients progressing or experiencing unacceptable toxicity should be taken off-study. A patient may be removed from study at any time at their request.

7.0 TOXICITY DEFINITIONS

7.1 Toxicity Criteria

The toxicity criteria that will be followed will be those of the NCI.

7.2 Death On Study

If a patient expires while on study, autopsy data, when available, will be used to correlate with the clinical data.

8.0 STUDY PARAMETERS

Patients will be evaluated weekly for the duration of time they remain on study and/or as clinically indicated.

Parameters	Initial[α]	Day 1,3 of Rx[β,χ]	qwk	End Rx	2 months post-Rx	post-Rx F/U[γ]
History and Physical Exam	x		x	x	x	x[γ]
Weight	x		x	x	x	
Performance Status	x		x	x	x	x[γ]
Tumor Measurement (clinical)	x		x	x	x	x[γ]
CBC & Differential	x	x	x	x	x	x[γ]
Electrolytes, BUN, creatinine	x	x	x	x		
Total Protein/Albumin	x					
Calcium/Phosphate/LDH,Uric Acid	x	x	x	x		
Bilirubin, Total, SGOT & SGPT	x	x	x	x		
Complement Levels	x	x				
Immunoglobulins, DAT	x				x	
Chest Xray	x					
CT of Chest, Abdomen, Pelvis	x				x	
Bone marrow asp/biopsy	x[δ]				x[δ]	
Flow Cytometry (PB/BM)	x				x	
Pharmacokinetic Studiesϕ	x.....see below for times.....				x	
Quality of Life Assessment	x		x	x	x	

α- Initial assessment may be performed within 10 days of starting treatment.

β-These laboratory parameters will be done pre-treatment and immediately post-treatment

χ- Two heparinized 10 cc tubes for cellular pharmacodynamics and cytokine studies at pre-treatment and at 2, 4, and 6 hours following initiation of rituximab infusion and at the time of any reaction requiring medical intervention (i.e. meperidine or cessation of infusion) for the first two treatments.

δ- Unilateral for CLL; Bilateral for SLL

ε- For SLL/CLL patients without disease involvement at this site at diagnosis, this is not required

ϕPharmacokinetic studies will be done prior to and after each dose of rituximab during the first week of treatment, weekly (prior to and after treatment on Friday) thereafter during treatment and then 1 day, 3 days, 7 days, 4 weeks and 8 weeks after rituximab treatment. Pre and post treatment assessement for HACA will occur.

γ-For patients responding to therapy, follow-up will be every 3 months for the first year after which they go off study. During follow-up, a CBC and physical exam should be performed to assess disease status. Other studies (i.e. CT and bone marrow studies) are left to the discretion of the treating physician.

9.0 PHARMACOLOGY STUDIES

9.1 Cellular Pharmacodynamics of Rituximab

In this study of rituximab, an anti-CD20 monclonal antibody, the potential to correlate anti-tumor responses with the cellular pharmacodynamics of this agent is attractive. In the present study the pharmacodynamics of rixuximab will be assessed prior to and during the first two treatments with rituximab.

The following cellular pharmacodynamic assays will be performed:

- To correlate quantitative CD20 expression with response to rituximab, CD20 will be assessed pre-treatment in all patients with assessable tumor cells. An identical sample will be obtained at the 2 month post-treatment evaluation. Two 5cc bone marrow and 10 cc peripheral blood heparinized (ie green top) tubes will be obtained at each of these times. These should be sent to Charlotte Shinn M.S., Johns Hopkins Oncology Center, Room 3-127. Flow cytometry samples will be analyzed and the remaining cells alloquoted and cryopreserved for possible future non-germ line studies.

- In an attempt to determine the etiology of initial infusion related side effects of rituximab, plasma will be obtained from patients prior to, 2, 4, and 6 hours following initiation of rituximab. Additionally, plasma samples will be obtained at the time of an adverse infusion reaction. We will attempt to document in vivo and ex vivo apoptosis utilizing either the annexin-V assay or a mitochondrial mass/membrane potential assay from isolated mononuclear cells and changes in apoptosis selected proteins using standard Western Blot methodology. MRNA changes may also be assessed using Northern Blot techniques or CDNA microarray technology. Plasma samples will be frozen at -70°C and assessed for various cytokine levels (TNF-alpha, IL-1, IL-2, IL-6, IL-8, interferon-gamma). These assays will be performed using electrochemilumenescence that allows detection at a level of 10 picograms/ml. These studies will be performed in the laboratory of Dr. Geofrey Ling at USUHS. 7 cc of heparinized blood (i.e. green top tube) should be drawn at the appropriate time points and immediately placed on ice. Plasma isolated should be divided into six vials equally and immediately transferred to a -70 °C freezer. All samples should list the patient's name, cycle of therapy (i.e. 1 or 2), treatment time (i.e. pre-treatment, 2 hours, 4 hours, 6 hours, or time of infusion-related toxicity), date/clock time of phlebotomy, and date/clock time sample is placed in -70 ° C freezer.

9.2 Pharmacokinetic Studies

Blood serum samples will be obtained at the following time points: pretreatment and post treatment during the first week of rituximab treatment and thereafter pre-treatment and post-treatment on the Friday treatment. Blood samples will be obtained 24 hours,

72 hours, 1 week, 4 weeks and 8 weeks after completion of therapy. Serum levels of drug will be measured in the first 3 patients treated in the study and any necessary adjustments to the sampling scheme will be made. Pharmacokinetic studies will be performed in the IDEC Pharmaceutical laboratory directed by Dr. Rosenberg.

10.0 TUMOR RESPONSE CRITERIA

Criteria For Response and Progression

Criteria for response will utilize the Revised National Cancer Institute-sponsored Working Group Guidelines for response which includes clinical, hematologic, and bone marrow features as outlined below (41).

10.1 Complete response: Requires all of the following for a period of at least two months from completion of therapy:

- Absence of lymphadenopathy on physical exam;
- No hepatomegaly or splenomegaly on physical exam;
- Absence of constitutional symptoms;
- Normal CBC as exhibited by polymorphonuclear leukocytes $\geq$ 1500/μL, platelets > 100,000/μL, hemoglobin > 11.0 g/dl (untransfused); lymphocyte count < 5,000/μL;
- Bone marrow aspirate and biopsy must be normocellular for age with <30% of nucleated cells being lymphocytes. Lymphoid nodules must be absent. If the marrow is hypocellular, a repeat determination should be performed in one month.
- Patients who fulfill the criteria for CR after induction with the exception of a persistent cytopenia that is believed to be treatment related will be considered a partial response. Additionally, patients who fullfill the criteria of CR with exception of having bone marrow lymphoid nodules will be considered a partial response.

10.2 Partial response:

- Requires a $\geq$ 50% decrease in peripheral lymphocyte count from pre-treatment value, $\geq$50% reduction in lymphadenopathy, and/or = 50% reduction in splenomegaly/hepatomegaly for a period of at least two months from completion of therapy. Additionally, these patients must have one of the following:
- Polymorphonuclear leukocytes > 1,500/μL or 50% improvement from pre-treatment value;
- Platelets > 100,000/μL or 50% improvement from pre-treatment value;

- Hemoglobin > 11.0 g/dl (untransfused) or 50% improvement from pre-treatment value.

10.3 Progressive Disease: Characterized by any one of the following events:

- >50% increase in the products of at least two lymph nodes on two consecutive determinations two weeks apart (at least one lymph node must be > 2 cm); appearance of new palpable lymph nodes.
- >50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly, which was not previously present.
- >50% increase in the absolute number of circulating lymphocytes to at least 5,000/μL.
- Transformation to a more aggressive histology (i.e., Richter's syndrome or prolymphocytic leukemia with = 56% prolymphocytes.

11.0 FORMS TO BE KEPT

On study as well as follow-up data will be recorded on data sheets specific to this study (Appendix 3). These should be submitted to Kathy Park R.N., Hematology-Oncology Service, Ward 78, Walter Reed Army Medical Center, Washington D.C. 20307 (FAX 202-782-9243) within 1 month of completion of therapy

Before activation at specific institutions, the protocol will have been reviewed and approved by the Clinical Research Committee of The Johns Hopkins Oncology Center, The Joint Committee on Clinical Investigations of The Johns Hopkins University, Institutional Review Board of Walter Reed Army Medical Center, and IDEC Pharmaceuticals/Genentech, Incorporated. All study participants must sign an informed consent which will describe the objectives of the study and potential risks. All patient data reported on the case report forms will be identified by the patient's initials and study code number only. Patients shall not be identified by name.

12.0 ASSESSMENT OF SAFETY/REPORTING OF SERIOUS ADVERSE EVENTS

12.1 Assessment of Safety

The safety of Rituximab will be assessed through collection and analyses of adverse events (AEs), baseline medical conditions, laboratory tests, and vital sign data.

12.2 Recording Adverse Events

All protocol-defined adverse events (AEs) encountered during the course of the study should be recorded on the appropriate AE pages of the Case Report Form (CRF).

For this protocol, an AE is any untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness, abnormal laboratory finding) that emerges or worsens relative to pretreatment baseline during the course of the study, regardless of the suspected cause. Note: Any medical condition present at the initial visit (i.e., prior to any study drug exposure), which remains unchanged or improves, should not be recorded as an AE at subsequent visits. However, if there is **deterioration** of a medical condition that was present at the initial visit, then this should be considered a **new** AE and recorded.

12.3 Adverse Events Requiring Expedited Reporting

Serious Adverse Events (SAEs) considered associated with Rituximab should be reported to the Study Coordinating Center/Principal Investigator within 48 hours of observing or learning of the event. Refer to Section 5.2 [Adverse Events] for medical events that are not considered AEs for this study.) The definitions for "serious" and "associated" are as follows:

Serious Adverse Event (SAE)

- Results in death (i.e., the AE caused or led to death); or
- Is life threatening (i.e., the AE placed the subject at immediate risk of death; and/or
- Requires or prolongs inpatient hospitalization (i.e., the AE required at least a 24-hour inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion); and/or
- Is disabling (i.e., the AE resulted in a substantial disruption of the subject's ability to carry out normal life functions); and/or
- Is a congenital anomaly/birth defect (i.e., an adverse outcome in a child or fetus of a subject exposed to rituximab prior to conception or during pregnancy); or
- Does not meet any of the above serious criteria but may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Associated

For reporting purposes, an AE should be regarded as associated with the use of Rituximab if the investigator believes:

- There is a clinically plausible time sequence between onset of the AE and Rituximab administration; and/or
- There is a biologically plausible mechanism for Rituximab causing or contributing to the AE; and

- The AE may or may not be attributed to concurrent/underlying illness, other drugs, or procedures.

To be conservative, any unusual or unexpected reaction should be considered associated with the use of Rituximab.

12.4 How to Report Associated SAEs

All SAEs considered associated with the use of Rituximab should be recorded on a MedWatch 3500 Form (see Appendix 18.7).

Participating investigators should report all associated SAEs to the Coordinating Center/Principal Investigator within 48 hours of observing or learning of the event. The completed MedWatch 3500 Form should be faxed to:

Tom Maneatis, M.D.
Genentech Drug Safety
Tel: (650) 225-2261
Fax: (650) 225-4683

Relevant follow-up information should be submitted to Genentech as soon as it becomes available.

Fatal or life-threatening events considered associated with Rituximab should be telephoned to the Medical Monitor immediately, in addition to completing the MedWatch 3500 Form.

Medical Monitor:	Lori Kunkel, M.D.
Telephone No.:	(650) 225-2132

13.0 RETURN OF STUDY DRUG

Genentech, Incorporated will be contacted with regard to disposition of any extra drug left over from this trial.

14.0 APPROVAL OF THE STUDY

This study will become active when the final protocol has been approved by the appropriate institutional review boards, IDEC Pharmaceuticals and Genentech, Incorporated.

15.0 PROCEDURE FOR AMENDMENTS TO THE PROTOCOL

All revisions or amendments to the protocol must be approved by the appropriate institutional review boards, IDEC Pharmaceuticals, and Genentech, Incorporated.

16.0 STATISTICAL CONSIDERATIONS

The primary objective of this study is to determine the feasibility of administering rituximab in a thrice-weekly schedule to patients with CLL and SLL. It is anticipated that 2-3 patient per month will be enrolled in the study with an anticipated study duration 1.5 years (including follow-up). The 95% confidence interval for absence of DLT reduces as the sample size increases as outlined below:

no. pts.	# with toxicity	95% CI for 0%
3	0	0% to 63%
6	0	0% to 39%
10	0	0% to 26%

Thus, although the reason for including 4 additional patients in the recommended phase II dose cohort is for the correlative laboratory studies, this will allow us to have a narrower confidence interval around the observed frequency of DLT.

The pharmacokinetic and pharmcodynamic data analysis will be exploratory. For this reason, a total of 10 patients will be included in the final dose level to allow adequate characterization of change of each cytokine (IL-6, IL-8, TNF-alfa, Interferon-gamma). Controlling the probability of a Type I error at alpha+0.05, a sample of 10 subjects will have a 80% power to detect a change of one standard deviation (about 25% of the pre-treatment value) in quanitative cytokine levels. Changes in cytokines before and after treatment will be exaamined using the paired t-test or Wicoxon rank sum test, as appropriate. Other data will be described utilzing means +/- standard error of the mean.

In this study pharmacokinetic analysis will be performed using the nonlinear regression software program PCNONLIN (PCNONLIN, SCI Consultants, Apex NC). Scatterplots will be used to compare pharmacodynamic and pharmacokinetic endpoints. In this study the main pharmacodynamic effects are anticipated to be infusion-related toxicity and thrombocytopenia. Potential differences in the disposition of rituximab between male and female patients will be assessed using box plots of the values for each pharmacokinetic parameter, and Mann Whitney U test and t-test where appropriate. Statistical analysis will be performed using Statistica 5 for Windows software program (Statsoft, Tulsa OK).

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18.0 APPENDICES

18.1 ECOG and Karnofsky Performance Status

18.2 Case Report Forms

18.3 Informed Consent

18.4 NCI Toxicity Criteria

18.5 Criteria for Hematologic Toxicity in Patients with CLL

18.6 Suggested Teaching Form for Varicella Zoster

18.7 MedWatch 3500 Form

APPENDIX I

Eastern Cooperative Oncology Group
Performance Status Key

Scale	
0	Fully active
1	Restricted in physically strenuous activity
2	Ambulatory, capable of self-care, unable to work, 50% of waking hours are spent out of bed
3	Limited self-care, spends more than 50% of the time in bed
4	Completely disabled, no self-care

COMMON TOXICITY CRITERIA (CONTINUED)

TOXICITY	GRADE 0	1	2	3	4
Blood Pressure Hypotension	continued none or no change	changes requiring no therapy (including transient orthostatic hypotension)	requires fluid replacement or other therapy but not hospitalization	requires therapy and hospitalization resolves within 48 hrs of stopping the agent	requires therapy and hospitalization for >48 hrs after stopping the agent
Neurologic Neurosensory	none or no change	mild paresthesias loss of deep tendon reflexes	mild or moderate objective sensory loss moderate paresthesias	severe objective sensory loss or paresthesias that interfere with function	paralysis
Neuromotor	none or no change	subjective weakness, no objective findings	mild objective weakness without significant impairment of functions	objective weakness with impairment of function	
Neurocortical	none	mild somnalence or agitation	moderate somnalence or agitation	severe somnalence, agitation, confusion, disorientation, or hallucinations	coma, seizures, toxic psychosis
Neurocerebellar	none	slight incoordination, dysdiadokinesis	intension tremor dysmetria, slurred speech, nystagmus	locomotor ataxia	cerebellar necrosis
Neuromood	no change	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal ideations
Neuroheadache	none	mild	moderate or severe but transient	unrelenting and severe	–
Neuroconstipation	none or no change	mild	moderate	severe	ileus >96 hrs
Neurohearing	none or no change	asymptomatic, hearing loss on audiometry only	tinnitus	hearing loss interfering with function but correctable with hearing aid	deafness not correctable
Neurovision	none or no change	–	–	symptomatic subtotal loss of vision	blindness

COMMON TOXICITY CRITERIA (CONTINUED)

TOXICITY	GRADE 0	1	2	3	4
Kidney Bladder					
Creatinine	WNL	<1.5 X NL	1.5-3.0 X NL	3.1-6.0 X NL	>6.0 X NL
Proteinuria	no change	1 + or <0.3% or <3 g/l	2-3 + or 0.3-1.0 g% or 3-10 g/l	4 + or >1.0 g% or > 10 g/l	nephrotic syndrome
Hematuria	neg	micro only	gross no clots	gross & clots	requires transfusion
Alopecia	no loss	mild hair loss	pronounced or total hair loss	–	–
Pulmonary	none or no change	asymptomatic, with abnormality in PFT's	dyspnea on significant exertion	dyspnea at normal level of activity	dyspnea at rest
Heart					
Cardiac dysrhythmias	none	asymptomatic, transient, requiring no therapy	recurrent or persistent, no therapy required	requires treatment	requires monitoring, or hypotension, or ventricular tachycardia, or fibrillation
Cardiac Function	none	asymptomatic, decline of resting ejection fraction by <20% of baseline value	asymptomatic, decline of resting ejection fraction by >20% of baseline value	mild CHF, responsive to therapy	severe or refractory CHF
Cardiac – Ischemia	none	non-specific T-wave flattening	asymptomatic, ST and T-wave changes suggesting ischemia	angina without evidence for infarction	acute myocardial infarction
Cardiac– pericardial	none	asymptomatic effusion, no intervention required	pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage required	tamponade; drainage urgently required
Blood pressure					
Hypertension	none or no change	asymptomatic, transient increase by >20 mmHg (D) or to > 150/100 if previously WNL. No treatment required	recurrent or persistent increase by >20mmHg (D) or to >150/100 if previously WNL. No treatment required	requires therapy	hypertensive crisis

COMMON TOXICITY CRITERIA (CONTINUED)

TOXICITY	GRADE 0	1	2	3	4
Hemorrhage (clinical)	none	mild/no transfusion	gross, 1-2 units transfusion per episode	gross, 3-4 units transfusion per episode	massive >4 units transfusion per episode
Infection	none	mild	moderate	severe	life-threatening
Gastrointestinal Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	—
Vomiting	none	1 episode in 24 hours	2-5 episodes in 24 hours	5-10 episodes in 24 hours	>10 episodes 24 hrs or requiring parenteral support
Diarrhea	none	Increase of 2-3 stools/day, over pre-Rx	Increase of 4-6 stools/day, or nocturnal stools, or moderate cramping	Increase of 7-9 stools/day or incontinence, or severe cramping	Increase of ≥10 stools/day, or grossly bloody diarrhea, or the need for parenteral support
Stomatitis	none	painless ulcers erythema, or mild soreness	painful erythema, edema, or ulcers but can eat	painful erythema edema, or ulcer and cannot eat	requires parenteral or enteral support
Liver Bilirubin	WNL	—	<1.5 x nl	1.5-3.0 x nl	>3.0 x nl
Transaminase (SGOT, SGPT)	WNL	≤2.5 x nl	2.6-5.0 x nl	5.1-20.0 x nl	>20.0 x nl
Alkaline Phos or 5' nucleotidase	WNL	≤2.5 X NL	2.6-5.0 x nl	5.1-20.0 x nl	>20.0 x nl
Liver (clinical)	no change from baseline	—	—	precoma	-hepatic coma

Appendix **5**

Grading Scale for Hematological Toxicity in CLL Studies*

Decrease from Pretreatment value (%)	Grade[a] Platelets[b]	Hemoglobin[c]
No Change - 10%	0	0
11-2 + %	1	1
25-49%	2	2
50-75%	3	3
≥ 75%	4	4

*a decrease in circulating granulocytes is not being considered since it is not a reliable index in CLL.

[a]Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening. Grade 5 (fatal) toxicity can potentially occur at any level of decrease from pretreatment values and will be recorded as such.

[b]If, at any level of decrease the platelet count is < 20,000/μl, this will be considered grade 4, unless the initial platelet count is < 20,000, in which case the patient is inevaluable for toxicity referable to platelet counts.

[c]Baseline and subsequent hemoglobin determinations must be immediately prior to any given transfusions.

Date: Thu, 15 Jan 1998 21:47:53 -0500
From: John C Byrd <john_c.byrd@WRAMAA.CHCS.AMEDD.ARMY.MIL>
Subject: IDEC-C2B8 in CLL
To: john_c.byrd@WRAMAA.CHCS.AMEDD.ARMY.MIL, cwhite@idecpharm.com, khorvath@gene.COM

I am becoming increasingly excited about IDEC-c2b8 in CLL (particularlly the bright CD20 expressers) We have treated another patient with CLL PLL and a high bulk tumor with a very high WBC. We again saw rapid cell reduction during the immediate infusion with a rise in LDH but some rebound suggesting re-distribution. As I remember from the discussion that Susan O'Brien and I had at ASH, she was planning to do a dose escalation study on a weekly schedule. Although I don't have any pharmacokinetic data to support my hypothesis, the clinical experience we have had thus far with these two bulky tumor patients (as most symptomatic CLL patients will be) make me believe that a 2-3 x weekly schedule until depletion occurs (and half life prolongs) might be a better schedule to examine in CLL. (and potentially bulky NHL). A similar observation has held in CLL with the campath-1H monoclonal antibody where the 3 x weekly schedule was determined to be optimal over more spaced out schedules. I am not certain what your development plan is for CLL....our group (Walter Reed and Johns Hopkins) could potentially pilot this in a small number of patients if drug were supplied and you could perform the pharmacokinetic sample analysis. My greatest interest is to see the treatment of CLL foward rather than get stalled because we didn't think about ideal dose and scheduling Ideally, the dose identified by Susan as adequate or an alternative schedule (possibly the one above or another yet identified schedule) would be the best to use for phase II study of IDEC-C2B8 alone.

In that regard, we received our comments from CTEP regarding the CALGB study. They want a third arm supported (IDEC-C2B8 then fludarabine) but acknowledge that the ideal schedule is not known. Approval of the study utilizing NCI derived drug was contingent on this 3rd arm being included. discussions had occured between Dr. Larson and Dr. Cheson resulting in agreement that they will allow the study to move foward with two arms now if a third arm is added later. (when additional dosing/scheduling data is known) Adding this 3rd arm later would potentially increase the number of patients by 25. Would this be acceptable to you and the other scientists at IDEC? In this regard, anything you can do to help from your side to get things moving at the NCI would be great. On a third note, Dr. Larson is reviewing the completed PLL concept sheet we discussed which will be coming your way soon. Thanks for your assistance. I would welcome the opportunity to talk with you about these issues if you have questions.

Sincerely,

John C. Byrd M.D.
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Hematologic Oncology
Walter Reed Army Medical Center
202-782-3256

c.c. Kathy Horvath R.N.